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(54) Title: TAMOXIFEN AND TAMOXIFEN ANALOGUE GLYCOSIDES AND USES THEREOF

(57) Abstract: Glycosides and orthoester glycosides of tamoxifen and its analogues exhibit higher plasma levels than tamoxifen after oral administration.

TAMOXIFEN AND TAMOXIFEN ANALOGUE GLYCOSIDES AND USES THEREOF

The present invention relates to derivatives of tamoxifen and its analogues, and to the use thereof to treat conditions treatable with tamoxifen and its analogues.

Tamoxifen is an anti-oestrogenic agent that blocks the actions of oestrogens on target tissues. It is useful as a palliative treatment for certain patients with advanced breast cancer, and can also be used effectively as an adjuvant in the treatment of oestrogen-receptor containing breast tumours [*c.f.* Goodman and Gilman's "The Pharmacological Basis of Therapeutics," 8th edition, pp. 1256-1257 and 1395-1397, Gilman *et al.* (eds.), Pergamon Press, New York, NY (1990)].

Tamoxifen is a triarylene derivative having the same stilbene nucleus as diethylstilbestrol. Such triarylene derivatives can display either agonist or antagonist activity depending on the orientation of the alkylaminoethoxy side chain. In the *trans* configuration (of tamoxifen), the compounds are anti-oestrogens. In the *cis* configuration, they are agonists. In humans, both isomers can be activated metabolically by hydroxylation at C-4 of the A ring, producing phenolic metabolites with affinities for the oestrogen receptor that are 100-fold greater than those of the parent molecules. Although the isomers of tamoxifen are relatively stable, their metabolites isomerise readily to produce mixtures. This may explain why anti-oestrogenic properties observed *in vivo* do not always agree with those detected *in vitro* (Goodman and Gilman, *supra*).

Tamoxifen and derivatives thereof may be used, as appropriate, as: oestrogenic, anti-oestrogenic and progestanic agents (US-A-4,696,949); for imaging oestrogen receptors (with halo-substituted tamoxifen, US-A-5,192,525); treating a mammal for breast cancer, treating or preventing cardiovascular disease, treating or preventing osteoporosis (US-A-5,877,219); treating breast cancer (US-A-5,807,899); treating endometriosis, obesity, benign prostatic hypertrophy and prostatic carcinoma in mammals (US-A-5,852,059); treating oestrogen-dependent tumours such as breast cancer tumours (US-A-5,491,173);

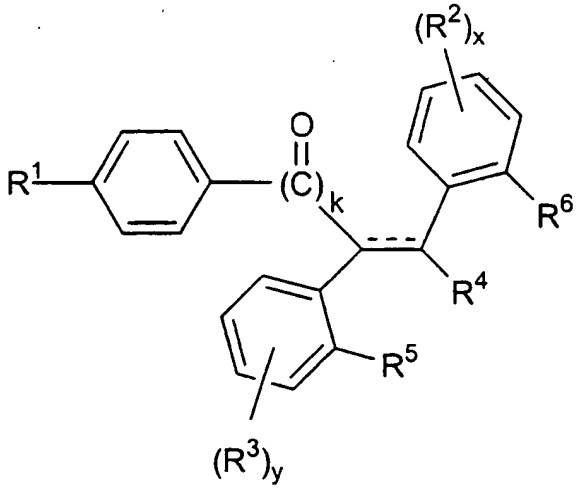
treating osteoporosis, pre-menstrual syndrome, vasomotor spasms associated with menopause, atrophic vaginitis, Kraurosis vulvae, female hypogonadism, primary ovarian failure, excessive hair growth and prostatic cancer (US-A-5,189,212); and treating psoriasis (US-A-4,851,433).

Various analogues of tamoxifen are known and are disclosed in U.S. Patent Nos. 5,877,219, 5,192,525, 5,196,435, 5,807,899 and 4,696,949, for example.

Unfortunately, despite the usefulness of tamoxifen in the treatment and prophylaxis of, particularly, breast cancer, it is associated with increased incidence of endometrial cancer, as evidenced by the increased thickening of the uterine wall. Accordingly, it is desired to identify a compound or compounds which have the advantages of tamoxifen, but which are less able to cause thickening of the uterine wall.

Surprisingly, it has now been found that the glycosides and orthoester glycosides of tamoxifen and its analogues have higher bioavailability than the parent compound.

In a first aspect, the present invention provides a compound of the Formula (I):



(I)

wherein

--- represents a single bond or a double bond;

k is 0 or 1;

R^1 is: i) H;

ii) $-(CH_2)_nCR^5=CR^6CR^7$

in which n is a number selected from 0, 1 and 2;

R^5 and R^6 are independently H, $-C_{1-4}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{2-4}$ alkynyl, $-X-C_{1-3}$ alkyl, $-X-C_{2-4}$ alkenyl, $-X-C_{2-4}$ alkynyl or -Y;

X is oxygen or sulphur and

Y is halogen, H, alkylcarbonyloxy, formyloxy or formyl;

R^7 is -CN, $-C_{1-4}$-haloalkyl, $-C_{1-4}$-alkyl-OH, $-C(O)NR^{10}R^{11}$, $-C(O)NR^{12}R^{13}$, $-C_{1-4}$-alkyl-$NR^{10}R^{11}$, $-C(O)R^{12}$, $-C(O)OR^{15}$, $-C(O)NR^{12}OR^{15}$, $-C(O)NHC(O)R^{12}$, $-C(O)NHCH_2R^{12}$, $-C(NH_2)(NOR^{15})$, $-S(O)R^{12}$, $-S(O)(O)(OR^{15})$, $-S(O)(O)N(H)(CO_2R^{15})$, PO_3R^{15}, $-P(O)(NR^{12}R^{13})(NR^{12}R^{13})$, $-P(O)(NR^{12}R^{13})(OR^{14})$, $-CONR^{12}(CH_2)_rOCH_3$, $-CONR^{12}(CH_2)_rNR^8R^9$ or oxadiazole optionally substituted with methyl;

R^8 and R^9 are independently hydrogen, $-C_{1-7}$alkyl, $-C_{3-7}$cycloalkyl, $-O-C_{1-7}$alkyl, $-C_{1-7}$alkyl-Y or phenyl, or, together, form a lower alkylene, a lower heteroalkylene, a lower alkenylene or lower heteroalkenylene group having from 3 to 6 atoms;

R^{10} and R^{11} are independently methyl or ethyl or, taken together, form a morpholino group bonded *via* its nitrogen atom;

R^{12} and R^{13} are independently H, $-C_{1-12}$alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, $-O-C_{1-12}$alkyl, $-O-C_{2-12}$alkenyl, $-O-C_{2-12}$alkynyl, $-C_{3-7}$cycloalkyl, $-C_{3-7}$cycloalkenyl, linear and cyclic heteroalkyl, aryl, heteroaryl or -Y';

R^{14} and R^{15} are independently hydrogen, $-C_{1-12}$alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, $-C_{3-7}$ cycloalkyl, $-C_{3-7}$ cycloalkenyl, linear and cyclic heteroalkyl, aryl, or heteroaryl;

r is an integer between 1 and 12, inclusive,

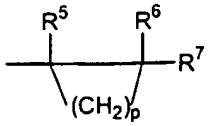
Y' is hydrogen, alkylcarbonyloxy, formyloxy or formyl;

iii) $-(CH_2)_mC(X)NR^8R^9$

in which X, R^8 and R^9 are as defined above and m is 1 or 2;

iv) $-X-(CH_2)_q-NR^8R^9$

in which X, R^8 and R^9 are as defined above and q is 1 or 2;

v) 

in which R^5, R^6 and R^7 are as defined above and p is an integer between 1 and 4, inclusive;

vi) -R-COOH

in which R is $-(CH_2)_tO-$ or $-(CH_2)_u-$ and *t* and *u* each represents an integer between 1 and 4, inclusive; or

vii) $-O-(CH_2)_v-A-S(O)_w-B-R^d$, in which

v is an integer between 1 and 10, inclusive,

A is either a direct bond or an amino bridge $-NR^c-$ or $-(CH_2)_l-$,

R^c is a hydrogen atom or a straight-chain or branched alkyl group with up to 6 carbon atoms and l is an integer between 1 and 5, inclusive;

w is 0, 1 or 2,

B is either a direct bond or a saturated or unsaturated, aliphatic, linear or branched hydrocarbon chain with up to 6 carbon atoms;

R^d is a hydrogen atom; a partially or completely fluorinated, saturated, aliphatic, linear or branched C_{1-3}-alkyl group; phenyl, or 1- or 2-naphthyl; an amide radical of formula $-C(O)NR^{16}R^{17}$ where R^{16} and R^{17} are identical or different and are a hydrogen atom, a linear or branched C_{1-8}-alkyl radical, optionally substituted by one or more radicals selected from aryl, alkyl- and dialkylamino, hydroxy, halogen or esterified carboxyl;

x is an integer between 1 and 4, inclusive;

each R^2 is the same or different and represents a halo, hydroxy, lower alkyl, lower hydroxyalkyl, lower haloalkyl or lower alkoxy group, or -OQ,

wherein Q is a straight or branched chain glycosidic residue or glycosidic

orthoester residue, or amino derivative thereof,

optionally with any two adjacent R^2 groups, or R^6 and the adjacent R^2, forming a buta-1,3-dienyl radical;

y is an integer between 1 and 4, inclusive;

each R^3 is the same or different and is H, halo, hydroxy, lower alkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkyl, or -OQ, where Q is as defined above, optionally with any two adjacent R^3 groups forming a buta-1,3-dienyl radical;

R^5 is as defined for R^3, or, together with R^4, represents a lower alkylene group, a lower alkylenoxy group, a lower alkylenesulphyl group, -S- or -O-;

R^6 is H, or is as defined for R^2, or, together with R^4, forms a trimethylene group or, together with R^4, forms a buta-1,3-dienyl radical, provided that - - - represents a single bond, R^5 optionally forming a bond to said radical, thereby forming a benzo[a]fluorene nucleus, and wherein any group formed by a combination of R^4 and R^6 is substituted by 0, 1, 2 or 3 R^2 groups;

with the proviso that at least one R^2 or one R^3 is a group -OQ;

R^4 is -CN, $-NO_2$, lower alkyl, lower alkyl substituted by Y, or -Y, in which Y is as defined above;

and pharmaceutically acceptable salts and esters thereof.

Compounds of the invention have been found to exhibit higher serum levels of the active, de-glycosylated hydroxy compound than either tamoxifen or 4-hydroxytamoxifen. For example, 4-hydroxytamoxifen-glucoside was able to prevent weight gain in oophorectomised animals and was more effective than tamoxifen. Thus, less of the compounds of the invention needs to be administered than tamoxifen or 4-

hydroxytamoxifen alone, as serum levels of active compound are higher, thereby further reducing any risk of the patient developing uterine neoplasms.

Without being bound by theory, it is believed that the glycosides and orthoester glycosides of the present invention yield the active compound only after passing through the liver, unlike tamoxifen and 4-OH tamoxifen, which suffer substantial first-pass degradation in the liver before reaching the general circulation.

Thus, the compounds of the present invention serve as protected precursors of the active tamoxifen or analogue. The glycoside or orthoester glycoside group is cleaved *in situ* to yield the active compound. The glycoside grouping is cleaved before the hydroxy tamoxifen or analogue can be metabolised, thereby protecting the active compound from first pass metabolism in the liver and making it available in the general circulation.

The present invention further provides pharmaceutical compositions comprising one or more compounds of the invention and one or more pharmaceutically acceptable carriers therefor.

There is further provided one or more compounds of the present invention for use in the treatment and/or prophylaxis of a condition susceptible of treatment by tamoxifen, especially those indicated herein and below.

Also envisaged are methods for the treatment and/or prophylaxis of conditions wherein tamoxifen may be indicated, especially which are selected from cardiovascular disease, osteoporosis, endometriosis, obesity, benign prostatic hypertrophy, prostatic carcinoma, oestrogen-dependent tumours, oestrogen independent tumours, breast cancer, metastatic breast cancer, pre-menstrual syndrome, vasomotor spasms associated with menopause, atrophic vaginitis, Kraurosis vulvae, female hypogonadism, primary ovarian failure, excessive hair growth, and psoriasis, said method comprising administering to an animal having the condition an effective amount of a compound of the present invention.

The present invention further provides the use of a compound of formula (I), or salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of a condition wherein tamoxifen may be indicated, especially wherein said condition is selected from cardiovascular disease, osteoporosis, endometriosis, obesity, benign prostatic hypertrophy, prostatic carcinoma, oestrogen-dependent tumours, oestrogen independent tumours, breast cancer, metastatic breast cancer, pre-menstrual syndrome, vasomotor spasms associated with menopause, atrophic vaginitis, Kraurosis vulvae, female hypogonadism, primary ovarian failure, excessive hair growth, and psoriasis.

It is particularly preferred that the compounds of the present invention be used in the treatment or prophylaxis of oestrogen-dependent tumours, either indication being, individually, more preferred. It is preferred that such tumours are, breast tumours, or tumours deriving therefrom.

The preferred route of administration is *per os*.

As provided herein, the term "alkyl", alone or in combination, refers to a straight or branched chain, saturated, hydrocarbon group having from 1 to 7 carbon atoms, unless otherwise indicated. The term "lower alkyl" is used herein to indicate an alkyl group having from 1 to 4 carbon atoms, unless otherwise indicated. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, t-butyl, n-pentyl, 2-methylpentyl, n-hexyl, 4-methylhexyl, 3-ethylpentyl, and n-heptyl.

The term "haloalkyl" is defined herein as an alkyl group having one or more halo substituents. The halo substituents are preferably chosen from fluorine, chlorine, bromine and iodine.

The term "cycloalkyl" is defined herein to include cyclic hydrocarbon radicals having from 3 to 7 ring carbon atoms. Some exemplary cycloalkyl radicals include the cyclopropyl, cyclobutyl, cyclobutyl, and cyclopentyl groups. A preferred cycloalkyl group is cyclohexyl.

The term "aryl," alone or in combination, is defined herein as a wholly unsaturated, optionally substituted, monocyclic or polycyclic group, having from 6 to 14 carbon atoms, preferably a monocyclic or bicyclic group, *e.g.*, phenyl or naphthyl. Substituted aryl groups may be substituted, for example, with one or more and, in particular, one to three, substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkanoyl, alkylthio, alkylsulphinyl and alkylsulphonyl groups. Some exemplary aryl groups include phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-iodophenyl, 2-methylphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-trifluoromethylphenyl, 4-nitrophenyl, 3-acetoxyphenyl, 4-acetylaminophenyl, 2-methylthiophenyl, 8-hydroxynaphthyl, 6-isopropylnaphthyl, and the like.

The term "heteroaryl" is defined herein as for aryl above, but containing one or more heteroatoms in place of one or more carbon atoms. Typically, the heterocycle will be 5- or 6- membered ring containing one, two or three, preferably one or two, heteroatoms, to which a carbocyclic, especially monocyclic aryl, group may be attached. The heterocyclic, aromatic group, or heteroaryl, optionally carrying a fused benzene ring, for example, may optionally be substituted. Preferred substituents are selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulphinyl and alkylsulphonyl. There may be one or more substituents and, in particular, one to three substituents.

The term "halogen" is defined herein to include fluorine, chlorine, bromine and iodine.

The term "linear and cyclic heteroalkyl" are defined in accordance with the term "alkyl" with the suitable replacement of carbon atoms with a heteroatom, such as nitrogen, oxygen or sulphur, in a manner sufficient to render a chemically stable species.

Stereocentres exist in the compounds of the present invention. It will be appreciated that the present invention includes all such possible stereoisomers and

geometric isomers of Formula (I), including both racemic mixtures as well as, separately, optically active isomers.

When a compound of Formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, any intermediate, or a starting material, may be effected by any suitable method known in the art. See, for example, *Stereochemistry of Carbon Compounds* by E.L. Eliel (McGraw Hill, 1962) and *Tables of Resolving Agents* by S. H. Wilen. Additionally, in situations where tautomers of the compounds of Formula (I) are possible, the present invention includes all such tautomeric forms.

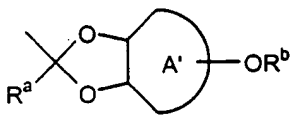
In general, the preferred compounds of Formula (I), and their salts and esters, fall into the following groups.

Those compounds where - - - represents a double bond are generally preferred. In such compounds, it is preferred that k = 0.

In those compounds where R4 and R5 together form a group, then it is preferred that - - - represents a single bond. In such compounds, it is also preferred that k = 1.

In general, it is preferred that Q contains 1-20 glycosidic units.

When Q is an orthoester glycoside, then it will generally be of the Formula (II):



(II)

wherein A' represents a glycofuranosyl or glycopyranosyl ring;

R_a is H, C_{1-4} alkyl, C_{7-10} aralkyl, phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, C_{1-4} alkyl or C_{1-4} alkoxy, or is naphthyl; and

R_b is H or a straight or branched chain glycosidic residue containing 1-20 glycosidic

units

In general, it is preferred that Q is glycosidic group, preferably a glycopyranosyl group, and particularly a 1′–β-glucopyranosyl group.

It is generally preferred that there is only one group R^2 and that it form the a group OQ. It is preferred that there be only one group OQ. When the group OQ is formed by R^2, then it is preferred that this group be in the 4' position on the phenyl group, or the equivalent geometric position on any multiple ring centre formed by any combination of groups R^2, R^3 and R^4.

When R^1 is $-(CH_2)_nCR^5=CR^6CR^7$, then it is preferred that n is 1 or 2 and R^5 and R^6 are H. In such compounds, it is preferred that R^7 is $-C(O)OR^{15}$, especially -COOH.

When R^1 is $-X-(CH_2)_q-NR^8R^9$, then it is preferred that X is O and that, preferably, q = 2. In such compounds, it is preferred that R^8 and R^9 are each methyl or ethyl, or that R^8 and R^9 together with the N to which they are joined, represent a piperidinyl or pyrrolidinyl group.

In general, it is preferred that y is 1. Preferred groupings for R^3 are hydroxy and iodo. When R^3 is -OQ then it is preferably in the 4' position.

Other preferred compounds are those wherein R^6 together with R^4 forms a trimethylene group, a buta-1,3-dienyl radical or where R^6 together with R^4 and R^5 forms a benzo[a]fluorene nucleus, or two groups R^2, or one R^2 group and one R^6 group help to form a naphthyl group. In such compounds, it is preferred that there is no, or one, R^2 substituent on the supplementary ring or rings so formed.

In general, it is preferred that R^4 is methyl or ethyl or, alternatively, is a chlorine atom, chloromethyl or chloroethyl group.

In preferred compounds of the invention:

R^1 is -Z-$(CH_2)_q$-NR^8R^9, where q is 2, Z is oxygen,

either R^8 is H or a lower alkyl radical and R^9 is a lower alkyl radical, or R^8 and R^9 are joined together with the adjacent nitrogen atom to form a heterocyclic radical, preferably pyrrolidinyl or piperidinyl;

R^4 is H or lower alkyl;

R^2 is -OQ;

R^3 is H or OH.

More preferably, R^8 and R^9 are both the same lower alkyl radical, especially methyl; R^4 is a lower alkyl radical, especially ethyl; R^2 is -O-glucosyl; and R^3 is OH.

Especially preferred compounds of Formula (I) include, individually, without limitation:

1-[4-(2-dimethylaminoethoxy)phenyl]-1-(4-O-β-1'-glucopyranosylphenyl)-2-phenylbut-1-ene,

1-[4-(2-dimethylaminoethoxy)phenyl]-1-(3-O-β-1'-glucopyranosylphenyl)-2-phenylbut-1-ene, and

4-chloro-1-[4-(dimethylaminoethoxy)phenyl]-1-(4-O-β-1'-glucopyranosyl- phenyl)-2-phenylbut-1-ene;

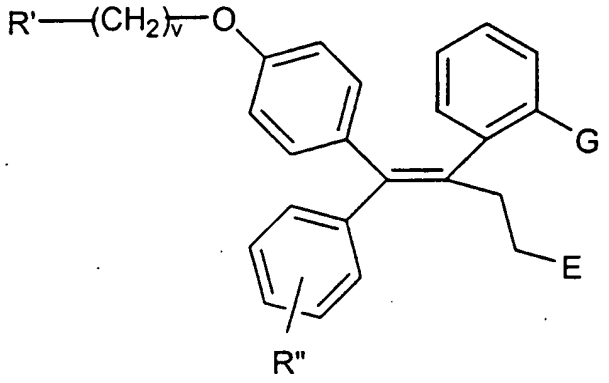
and the pharmaceutically acceptable salts and esters thereof.

It will be appreciated that, while the present invention extends to all compounds of formula (I) and salts and esters thereof, those compounds formulated for pharmaceutical use should be pharmaceutically acceptable, as formulated. Compounds which do not fall into this category may be employed in the synthesis of compounds which do, for example.

Other preferred compounds include the glycosides and orthoester glycosides of the hydroxy metabolites, derivatives and analogues of clomiphene, naloxifene, trioxifene, idoxifene, raloxifene, droloxifene, GW 5638, levormeloxifene and centchroman. Particular, individual, examples include (E)-1-(4-iodophenyl)-2-(4-O-β-1'-

glucopyranosylphenyl)-1-[4-(pyrrolidinoethoxy)phenyl]but-1-ene (the glucoside of a hydroxy derivative of idoxifene), 1-{4-[2-(diethylamino)ethoxy]phenyl}-2-(4-O-β-1'-glucopyranosylphenyl)-1-phenyl-2-chloroethenylene (the glucoside of a hydroxy derivative of clomiphene), [3,4-dihydro-2-(4-O-β-1'-glucopyranosylphenyl)-1-naphthalenyl]{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}methanone [the glucoside of a dihydroxy derivative related to trioxifene, see Jones, C.D. *et al., J. Med. Chem. 35:*931-938 (1992)]; 11-{4-[2-(1-piperidinyl)ethoxy]phenyl}-11*H*-3-(O-1'-β'-glucopyranosyl)benzo[a]fluorene-9-ol and 11-{4-[2-(1-piperidinyl)ethoxy]phenyl}-11*H*-benzo-[a]fluorene-3-ol-9-O-β'-glucopyranoside; and trans-1-{2-[4-(7-O-1'-β-glucopyranosyl-2,2-dimethyl-3-phenyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)phenoxy]ethyl}pyrrolidine (centchroman-7-O-glucoside).

A further group of preferred compounds are the triphenylethylenes, described in US-A-5,807,899, of the Formula (III):



(III)

wherein:

R' is a group of formula:

$$—A—S(O)_w—B—R^d$$

and v, A, w, B and R^d are as defined above,

R" is a hydrogen atom, an iodine atom, a hydroxy group or OQ;

E is a hydrogen atom;

G is as defined for R^2 or forms a methylene bridge with E;

or a pharmaceutically acceptable salt or ester thereof.

Useful pharmaceutically acceptable salts include acid addition salts, *e.g.*, salts with inorganic acids such as HCl, HBr, sulphuric, sodium hydrogen sulphate, phosphoric acid, sodium dihydrogen phosphate, and disodium hydrogen phosphate, as well as salts with organic acids such as formic, acetic, benzoic, carbonic and the like. Where the compound is substituted by a carboxy group, pharmaceutically acceptable salts may be obtained with an inorganic base such as an alkali or alkaline earth metal hydroxide [*e.g.* LiOH, NaOH, KOH, or $Ca(OH)_2$] or an organic base such as choline hydroxide, spermidine, spermine, glucamine and the like.

The compounds of the present invention may be used according to well-known methods of using tamoxifen and derivatives thereof, *e.g.* for use as oestrogenic, anti-oestrogenic and progestanic agents; for imaging oestrogen receptors (with halo-substituted derivatives); treating or preventing cardiovascular disease, treating or preventing osteoporosis; treating endometriosis, obesity, benign prostatic hypertrophy and prostatic carcinoma in mammals; treating oestrogen-dependent tumours such as breast cancer tumours; treating pre-menstrual syndrome, vasomotor spasms associated with menopause, atrophic vaginitis, Kraurosis vulvae, female hypogonadism, primary ovarian failure, excessive hair growth and prostatic cancer; and treating psoriasis. The compounds may be used to treat any one of these conditions or may be used prophylactically.

The compounds of the invention may be co-administered together with other compounds, *e.g.*, 9-*cis*-retinoic acid and derivatives thereof, to treat cancer, in particular, breast cancer (US-A-5,821,254); interferon to treat breast cancer (US-A-5,024,833); epinephrine, norepinephrine or dopamine to modify vasoconstrictive activity (US-A-5,470,883); melatonin and derivatives thereof to treat breast cancer (US-A-5,196,435); a platinum anti-neoplastic compound to treat non-melanoma cancers (US-A-5,844,001); a bone growth factor to stimulate new bone formation (US-A-5,118,667); ONCONASE™ to treat human pancreatic adenocarcinoma and human lung carcinoma (US-A-5,540,925); Raloxifene and derivatives thereof to treat mammary cancers and other conditions (US Patent no's 4,656,187,(US-A-4,656,187, 5,567,820, 5,512,296, 5,508,292, 5,496,851, 5,496,828, 5,492,927, 5,447,941, 5,534,526, 5,530,010, 5,525,624, 5,521,214, 5,521,198,

5,641,790, 5,622,975, 5,610,168, 5,610,167, 5,610,166, 5,591,753, 5,552,417, 5,552,416, 5,550,123, 5,545,641, 5,646,137, 5,663,184, 5,672,610, 5,686,467, 5,686,476, 5,688,812, 5,698,572, 5,700,815, 5,708,010, 5,770,612, 5,494,920, 5,686,468, 5,843,962, 5,578,614, 5,446,053, 5,693,656, 5,843,964, 5,593,987, 5,843,984, 5,510,358, 5,484,797, 5,610,167, 5,578,614, 5,843,914, 5,770,612, 5,698,572, 5,693,656, 5,552,416, 5,502,074, 5,492,927, 5,447,941, 5,441,964, 5,439,931, 5,418,252, 5,726,168, 5,843,984, 5,827,844, 5,808,061); an androstene derivative to treat an androgen responsive condition (US-A-5,846,976); a tissue factor pathway inhibitor to induce or augment tissue factor expression or release in a tumour tissue (US-A-5,902,582); a progesterone antagonist for hormone substitution therapy for peri-menopausal and postmenopausal women (US-A-5,719,136); a non-steroidal anti-oestrogen compound for inhibiting hormone-dependent breast carcinoma in a mammal (US-A-5,658,831); a compound having antiprogestational activity to induce labour, terminate pregnancy, or treat gynaecological disorders (US-A-4,888,331); aminoalkyl ethers of phenols to treat breast or colon cancer in humans (US-A-4,803,227); and an anti-androgen for prophylaxis and therapy of prostate hypoplasia (US-A-4,310,523).

By glycosidic units are meant glycopyranosyl or glycofuranosyl, as well as their amino sugar derivatives. The residues may be homopolymers, random or alternating polymers, or block copolymers of these monomers. The glycosidic units have free hydroxy groups, or the hydroxy groups may be acylated, *e.g.* with a group R^{16}–(C=O)-, wherein R^{16} is hydrogen, lower C_{1-6} alkyl, C_{6-10} substituted or unsubstituted aryl or C_{7-16} aralkyl. Preferably, the acyl groups are acetyl or propionyl. Other preferred R_{16} groups are phenyl, nitrophenyl, halophenyl, lower alkyl substituted phenyl, lower alkoxy substituted phenyl and the like or benzyl, lower alkoxy substituted benzyl and the like.

The compounds particularly useful in the practice of the invention contain at least one glycoside or orthoester glycoside residue on the A ring of the compound, by analogy with tamoxifen. In the case of tamoxifen, it is preferably the case that the glycoside, or orthoester glycoside, is linked through the 1-carbon to a 4-hydroxy group introduced on the A ring.

Any such glycoside can comprise up to 20 glycosidic units. Preferred, however, are those having less than 10 and, most preferred, are those having 3 or less glycosidic units. Specific examples are those containing 1 or 2 glycosidic units in the glycoside residue.

The glycopyranose or glycofuranose ring, or amino derivative thereof, may be fully or partially acylated or completely deacylated. The completely or partially acylated glycoside is useful as a defined intermediate for the synthesis of the deacylated material.

Among the possible glycopyranosyl structures are glucose, mannose, galactose, gulose, allose, altrose, idose, and talose. Among the furanosyl structures, the preferred ones are derived from fructose, arabinose and xylose. Among preferred diglycosides are sucrose, cellobiose, maltose, lactose, trehalose, gentiobiose, and melibiose. Among the triglycosides, the preferred ones may be raffinose or gentianose. The preferred amino derivatives are N-acetyl-D-galactosamine, N–acetyl-D-glucosamine, N–acetyl-D-mannosamine, N–acetylneuraminic acid, D-glucosamine, lyxosylamine, D-galactosamine, and the like.

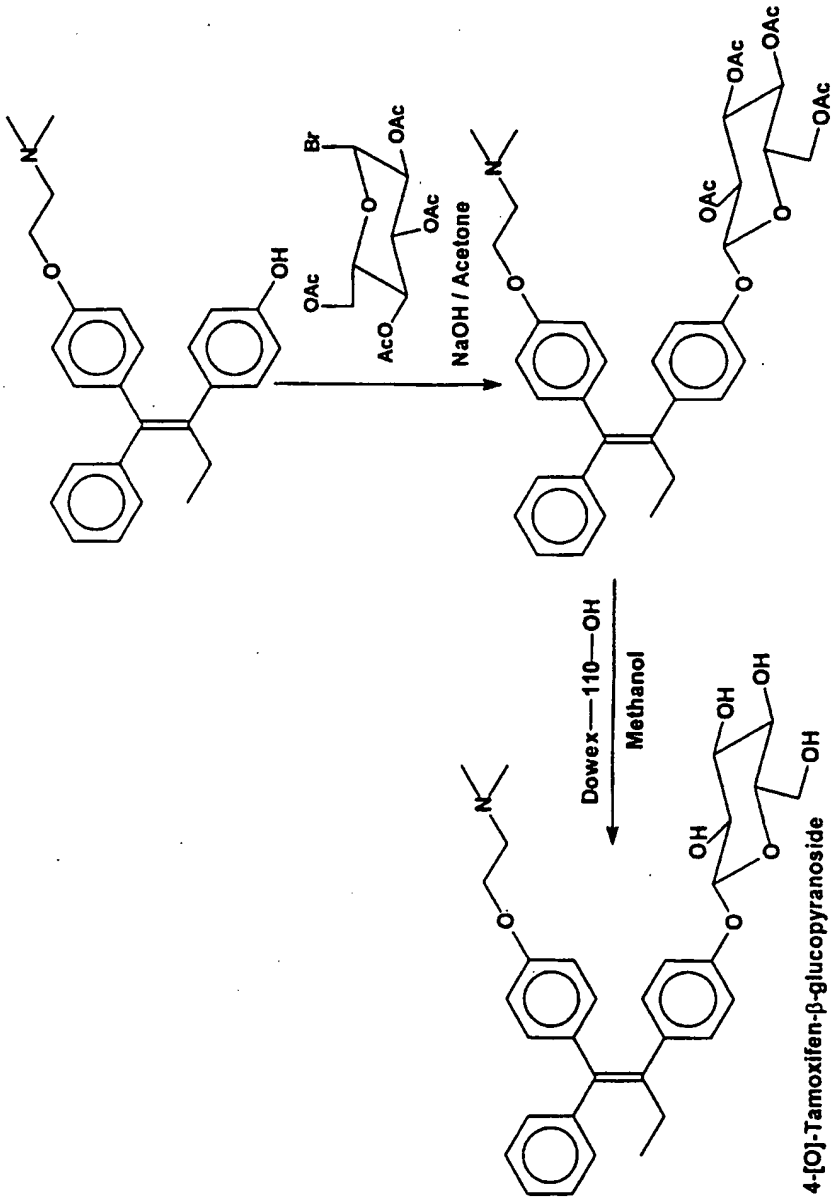
When more than one glycosidic unit is present on a single hydroxy group, *i.e.*, di- or polyglycosidic residues, the individual glycosidic rings may be bonded by 1-1, 1-2, 1-3, 1-4, 1-5 or 1-6 bonds, most preferably 1-2, 1-4 and 1-6. The linkages between individual glycosidic rings may be α or β.

The water soluble glycosidic derivatives of the aforementioned compounds may be obtained according to the general methods disclosed by Holick in US-A-4,410,515, the contents of which are fully incorporated by reference herein. The glycosyl orthoester compounds may be obtained according to US-A-4,521,410, the contents of which are also fully incorporated by reference herein.

A number of hydroxy-substituted analogues of tamoxifen are known and can be glycosylated according to the present invention. See US Patent No's. 5,877,219, 5,192,525,

5,196,435, 5,807,899 and 4,696,949. Scheme 1 below illustrates a general method of preparing the 4-glycosyl derivatives of tamoxifen.

Scheme 1


Br
OAc
OAc
AcO
OAc
O
NaOH / Acetone
OH
N
O
OAc
OAc
OAc
OAc
O
Dowex—110—OH
Methanol
OH
OH
OH
OH
4-[O]-Tamoxifen-β-glucopyranoside

Any animal which may benefit from the compounds described herein may be treated according to the present invention. Preferred animals are mammals, *e.g.* humans, although the invention is not intended to be so limited.

For oral administration, the compounds of the present invention may be administered in any appropriate pharmaceutically acceptable carrier, especially as the tamoxifen glycosides and derivatives thereof are biologically active upon oral administration. The compounds of the invention may also be administered in any appropriate pharmaceutical carrier for parenteral, such as intravenous or subcutaneous, intramuscular or topical, administration. They can be administered by any means that achieve their intended purpose.

The dosage administered will depend on the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. An exemplary systemic daily dosage is about 0.001 to about 100.0 mg/kg of body weight. Normally, from about 0.01 to about 10.0 mg/kg of body weight of the glycoside or orthoester glycoside, in one or more dosages per day, is effective to obtain the desired results. One of ordinary skill in the art can readily determine the optimal dosages and concentrations of the glycoside and orthoester glycoside compounds of the invention to administer.

The compounds can be employed in dosage forms such as tablets, capsules or powder packets, or liquid solutions, suspensions or elixirs for oral administration, as well as sterile liquid for formulations such as solutions or suspensions for parenteral use. A lipid vehicle can be used in parenteral administration. The compounds may also be administered *via* topical patches, ointments, gels or other transdermal applications, including for suppositories and pessaries. In such compositions, the active ingredient will ordinarily be present in an amount of at least 0.1% by weight based on the total weight of the composition, and not more than 90% by weight. An inert pharmaceutically acceptable carrier is preferable such as 95% ethanol, vegetable oils, propylene glycols, saline buffers,

sesame oil, *etc.* Reference is made to *Remington's Pharmaceutical Sciences*, 18th Edition, Gennaro *et al.* (eds.), 1990, for methods of preparing pharmaceutical compositions.

The compounds are preferably provided substantially pure prior to formulation. The phrase "substantially pure" encompasses compounds created by chemical synthesis and/or compounds substantially free of chemicals which may accompany the compounds in the natural state, as evidenced by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC).

The present invention will now be further illustrated by reference to the following Examples, which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

EXAMPLE 1

Organic Synthesis of 2',3',4',6'-Tetra-O-acetyl-1β-glucopyranosyl-4-0-Tamoxifen: (Tetra O-acetyl-4-0-β-1'-glucopyranoside)

Acetobromoglucose was purchased from Sigma and used without purification. 4-Hydroxy tamoxifen (Sigma) was used as such as a mixture of Z and E isomers (minimum 70% Z isomer).

4-Hydroxytamoxifen (50 mg, 0.129 nmol) in isopropanol-free acetone (1.5 ml) was cooled to 0°C under argon and stirred efficiently. Two solutions, one of acetobromoglucose (100 mg; 2.3-fold excess) in acetone (500 µl) and one aqueous solution of 13.3% w/w NaOH, were prepared freshly and kept cold. Five equal volumes of nearly 100 µl of acetobromoglucose solution were injected into the cold 4-hydroxytamoxifen over a period of 4 hours at equal intervals. Each of the bromoglucose injections was accompanied by 20 µl of 13.3% sodium hydroxide. After all the bromoglucose had been added, the mixture was warmed to room temperature and stirred for 30 minutes. Acetone

and water were removed by pump at low temperature. The resulting mixture was separated on a silica gel column. Ether and triethylamine (10:1) mixture was used as eluent. The less polar tetraacetate was removed from the column and crystallised from diethyl ether. It afforded 37 mg of crystalline white solid. The NMR spectra showed the presence of nearly 10-15% of E isomer –β–glucoside was present along with desired –Z-isomer–β–glucoside.

NMR:

δ (4.95; doublet, J=9.2Hz, E isomer, ~10-15% of 1 H);

δ (5.12; doublet, J=8.9Hz, Z isomer, 85-90% of 1 H);

δ (6.5-7.2; aromatic-H, 13 H);

δ (5.3 to 3.5; glucosyl-H, 9H);

δ (2.35-2.45; multiplet, 4H);

δ (2 to 2.2; overlapping singlets of N–CH_3 and acetate, 18H); and

δ 0.9 (triplet 3 H, CH_3).

The crude product obtained by recrystallisation was used as such without purifying E and Z isomers.

4-[O,1'–β-Glucopyranosyl]tamoxifen

To a solution of 2',3',4',6'-tetra-O-acetyl-1'-β-glucopyranosyl-4-O-tamoxifen (20 mg) in methanol (3 ml) were added 100 mg Dowex-110-OH resin. The mixture was refluxed for 4 hours in an inert atmosphere in the absence of light. After cooling and filtering the resin, the solvent was evaporated to a gum. Trituration with acetonitrile gave crystals. Yield 14.9 mg

38 mg of the crude glucoside obtained as above was crystallised from acetonitrile (0.5 ml). Crystals were collected by centrifuging and washing with fresh cold acetonitrile (2 x 500 µl). The white powder was dried under vacuum, which yielded (23 mg) of homogeneous white powder. The structure of this material was consistent with the spectral data.

UV: maxima at 243 nm and 279 nm.

Mass Spectra: Molecular formula $C_{32}H_{39}NO_7$ (gave molecular ion at 550.30 in formic acid consistent with structure).

NMR: (DMSO-d_6, 25°C),

δ (0.9, triplet; CH_3);

δ (2.2 & 2.65, $N(CH_3)_2$, singlets);

δ (2.4, quartet, CH_2);

δ (3.0-4.1, multiplets; 9 H);

δ (4.5-5.1, multiplets, 6 H);

δ (5.27, doublet, J=9H_Z, E isomer, anomeric H, and 5.35 doublet, J=8.8 H_Z ~90% of Z isomer); and

δ (6.6 to 7.3, multiplet, Aromatic-H, 13H).

Example 2

Synthesis of 4-[O,1'-β-Glucopyranosyl]tamoxifen

To a solution of 2',3',4',6'-tetra-O-acetyl-1'-β-glucopyranosyl-4-O-tamoxifen (20 mg) in methanol (3 ml) were added 100 mg Dowex-110-OH resin. The mixture was refluxed for 4 hours in an inert atmosphere in the absence of light. After cooling and filtering the resin, the solvent was evaporated to a gum. Trituration with acetonitrile gave crystals. Yield 14.9 mg

38 mg of the crude glucoside obtained as above was crystallised from acetonitrile (0.5 ml). Crystals were collected by centrifuging and washing with fresh cold acetonitrile (2 x 500 µl). The white powder was dried under vacuum, which yielded (23 mg) of homogeneous white powder. The structure of this material was consistent with the spectral data.

UV: maxima at 243 nm and 279 nm.

Mass Spectra: Molecular formula $C_{32}H_{39}NO_7$ (gave molecular ion at 550.30 in formic acid consistent with structure).

NMR: (DMSO-d_6, 25°C),

δ (0.9, triplet; CH_3);

δ (2.2 & 2.65, $N(CH_3)_2$, singlets);

δ (2.4, quartet, CH_2);

δ (3.0-4.1, multiplets; 9 H);

δ (4.5-5.1, multiplets, 6 H);

δ (5.27, doublet, J=9Hz, E isomer, anomeric H, and 5.35 doublet, J=8.8 Hz ~90% of Z isomer); and

δ (6.6 to 7.3, multiplet, Aromatic-H, 13H).

Example 3

Bioavailability of 4-Hydroxytamoxifen-Glucoside in Comparison to 4-Hydroxytamoxifen and Tamoxifen.

Rationale:

The goal of the study was to determine the bioavailability and bioactivity of 4-hydroxytamoxifen-glucoside, in oophorectomised female rats, in comparison to 4-hydroxytamoxifen and tamoxifen. This was to be accomplished by giving an equimolar dose of tamoxifen, 4-hydroxytamoxifen or 4-hydroxytamoxifen-glucoside to oophorectomised rats.

A daily a dose of tamoxifen, 4-hydroxytamoxifen, or 4-hydroxytamoxifen-glucoside, was administered to each rat over seven days. Body weights were determined and blood collected 24 hours after the last dose.

The goal was to determine the blood levels of 4-hydroxytamoxifen, 24 hours after the last dose, to determine whether the group that received 4-hydroxytamoxifen-glucoside was able to maintain higher blood levels of 4-hydroxytamoxifen.

Methodology:

Female rats of approximately 150 gm were oophorectomised and, seven days later, used for this study. The rats were equilibrated in their cages for 24 hours. Each rat in groups of four received a single oral dose, daily, of 1.5 mg equivalent of either tamoxifen, 4-hydroxytamoxifen, or 4-hydroxytamoxifen-glucoside. The blood was collected at the time of sacrifice for determination of 4-hydroxytamoxifen levels.

To evaluate the pharmacological effect of 4-hydroxytamoxifen-glucoside, three to four oophorectomised rats were dosed daily with either 1.5 mg equivalent of tamoxifen, 4-hydroxytamoxifen, or 4-hydroxytamoxifen-glucoside. The animals were weighed before they received the oral dose. At the time of sacrifice, 24 hours after the last dose on the seventh day, the animals were weighed and blood collected. The blood was used to determine 4-hydroxytamoxifen levels.

4-Hydroxytamoxifen was measured by high performance liquid chromatography using a straight phase Zorbax Sil column with a mobile phase of methanol : isopropanol : hexane (containing 0.1 % v/v triethylamine) = 10 : 10 : 80 (v/v/v). In this chromatographic system, 4-hydroxytamoxifen-glucoside does not elute. The elution peak for 4-hydroxytamoxifen was confirmed by its characteristic ultraviolet absorption spectrum. The recovery of 4-hydroxytamoxifen was based on the recovery of ^{3}H-tamoxifen that was added to 0.5 ml of rat serum before it was extracted and chromatographed.

Results:

At day 0, the body weights were similar for all of the groups. 24 Hours after the last dose on day seven, the body weights of the animals receiving placebo showed a significant increase in weight gain compared to the groups that received

4-hydroxytamoxifen or 4-hydroxytamoxifen-glucoside. An evaluation of the blood levels of 4-hydroxytamoxifen 24 hours after receiving the last dose is shown in Figure 1. The blood levels of 4-hydroxytamoxifen were higher in the group that received 4-hydroxytamoxifen-glucoside compared to the group that received 4-hydroxytamoxifen. No detectable 4-hydroxytamoxifen was detected in the group that received tamoxifen.

Conclusions

Animals that received 4-hydroxytamoxifen and 4-hydroxytamoxifen-glucoside maintained their body weights at the same level as baseline (non-oophorectomised, no treatment). However, oophorectomised animals that received the placebo had a statistically significant increase of approximately 40 to 60 gm, as expected, as oophorectomy mimics the effects of menopause. The fact that 4-hydroxytamoxifen and 4-hydroxytamoxifen-glucoside maintained the body weights in the animals that received these compounds demonstrates the pharmacological action of the drug that mimics oestrogen on maintaining body weight.

Over seven days, the blood levels of 4-hydroxytamoxifen in the group that received 4-hydroxytamoxifen-glucoside were higher than the group that received 4-hydroxytamoxifen. This is consistent with the concept that 4-hydroxytamoxifen-glucoside is metabolised to 4-hydroxytamoxifen, thereby acting as a pro-drug. It slowly releases 4-hydroxytamoxifen into the circulation, thereby maintaining higher circulating levels 24 hours after the last dose, compared to the group that received 4-hydroxytamoxifen. The group that received tamoxifen had no detectable blood levels of 4-hydroxytamoxifen.

Summary:

It is clear that 4-hydroxytamoxifen-glucoside is bioavailable and is metabolised to 4-hydroxytamoxifen. Furthermore, 4-hydroxytamoxifen-glucoside has the same pharmacological effect as an equimolar dose of 4-hydroxytamoxifen in maintaining body

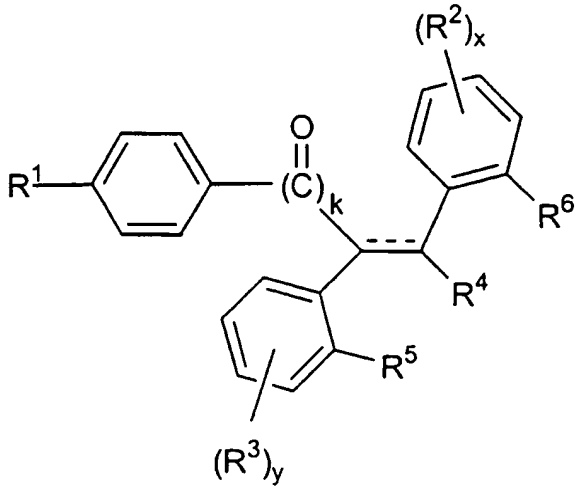
weight, but leads to higher blood levels of 4-hydroxytamoxifen in oophorectomised female rats.

Thus, 4-hydroxytamoxifen-glycoside acts as a pro-drug for the active form of tamoxifen (4-hydroxytamoxifen). Equimolar doses of 4-hydroxytamoxifen-glycoside and 4-hydroxytamoxifen yield similar amounts of 4-hydroxytamoxifen in the blood but, given that the glycoside does not all break down to the 4-hydroxy form straight away, then this shows that 4-hydroxytamoxifen has already been metabolised to a certain extent after administration, and that the glycoside is able to keep supplying the active form for longer. For long term treatment, this means less drug is necessary to achieve the same effect.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions without undue experimentation. All patents, patent applications and publications cited herein are incorporated by reference in their entirety.

CLAIMS:

1. A compound of the Formula (I):



(I)

wherein

--- represents a single bond or a double bond;

k is 0 or 1;

R^1 is: i) H;

ii) $-(CH_2)_nCR^5=CR^6CR^7$

in which n is a number selected from 0, 1 and 2;

R^5 and R^6 are independently H, $-C_{1-4}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{2-4}$ alkynyl, $-X-C_{1-3}$ alkyl, $-X-C_{2-4}$ alkenyl, $-X-C_{2-4}$ alkynyl or -Y;

X is oxygen or sulphur and

Y is halogen, H, alkylcarbonyloxy, formyloxy or formyl;

R^7 is -CN, $-C_{1-4}$-haloalkyl, $-C_{1-4}$-alkyl-OH, $-C(O)NR^{10}R^{11}$, $-C(O)NR^{12}R^{13}$, $-C_{1-4}$-alkyl-$NR^{10}R^{11}$, $-C(O)R^{12}$, $-C(O)OR^{15}$, $-C(O)NR^{12}OR^{15}$, $-C(O)NHC(O)R^{12}$, $-C(O)NHCH_2R^{12}$, $-C(NH_2)(NOR^{15})$, $-S(O)R^{12}$, $-S(O)(O)(OR^{15})$, $-S(O)(O)N(H)(CO_2R^{15})$, PO_3R^{15}, $-P(O)(NR^{12}R^{13})(NR^{12}R^{13})$, $-P(O)(NR^{12}R^{13})(OR^{14})$, $-CONR^{12}(CH_2)_rOCH_3$,

$-CONR^{12}(CH_2)_rNR^8R^9$ or oxadiazole optionally substituted with methyl;

R^8 and R^9 are independently hydrogen, $-C_{1-7}$alkyl, $-C_{3-7}$cycloalkyl, $-O-C_{1-7}$alkyl, $-C_{1-7}$alkyl-Y or phenyl, or, together, form a lower alkylene, a lower heteroalkylene, a lower alkenylene or lower heteroalkenylene group having from 3 to 6 atoms;

R^{10} and R^{11} are independently methyl or ethyl or, taken together, form a morpholino group bonded *via* its nitrogen atom;

R^{12} and R^{13} are independently H, $-C_{1-12}$alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, $-O-C_{1-12}$alkyl, $-O-C_{2-12}$alkenyl, $-O-C_{2-12}$alkynyl, $-C_{3-7}$cycloalkyl, $-C_{3-7}$cycloalkenyl, linear and cyclic heteroalkyl, aryl, heteroaryl or -Y';

R^{14} and R^{15} are independently hydrogen, $-C_{1-12}$alkyl, $-C_{2-12}$alkenyl, $-C_{2-12}$alkynyl, $-C_{3-7}$ cycloalkyl, $-C_{3-7}$ cycloalkenyl, linear and cyclic heteroalkyl, aryl, or heteroaryl;

r is an integer between 1 and 12, inclusive,

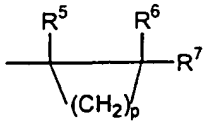
Y' is hydrogen, alkylcarbonyloxy, formyloxy or formyl;

iii) $-(CH_2)_mC(X)NR^8R^9$

in which X, R^8 and R^9 are as defined above and m is 1 or 2;

iv) $-X-(CH_2)_q-NR^8R^9$

in which X, R^8 and R^9 are as defined above and q is 1 or 2;

v) 

in which R^5, R^6 and R^7 are as defined above and p is an integer between 1 and 4, inclusive;

vi) -R-COOH

in which R is $-(CH_2)_tO-$ or $-(CH_2)_u-$ and *t* and *u* each represents an integer between 1 and 4, inclusive; or

vii) $-O-(CH_2)_v-A-S(O)_w-B-R^d$, in which

v is an integer between 1 and 10, inclusive,

A is either a direct bond or an amino bridge $-NR^c-$ or $-(CH_2)_l-$,

R^c is a hydrogen atom or a straight-chain or branched alkyl group with up to 6 carbon atoms and l is an integer between 1 and 5, inclusive;

w is 0, 1 or 2,

B is either a direct bond or a saturated or unsaturated, aliphatic, linear or branched hydrocarbon chain with up to 6 carbon atoms;

R^d is a hydrogen atom; a partially or completely fluorinated, saturated, aliphatic, linear or branched C_{1-3}-alkyl group; phenyl, or 1- or 2-naphthyl; an amide radical of formula $-C(O)NR^{16}R^{17}$ where R^{16} and R^{17} are identical or different and are a hydrogen atom, a linear or branched C_{1-8}-alkyl radical, optionally substituted by one or more radicals selected from aryl, alkyl- and dialkylamino, hydroxy, halogen or esterified carboxyl;

x is an integer between 1 and 4, inclusive;

each R^2 is the same or different and represents a halo, hydroxy, lower alkyl, lower hydroxyalkyl, lower haloalkyl or lower alkoxy group, or -OQ,

wherein Q is a straight or branched chain glycosidic residue or glycosidic orthoester residue, or amino derivative thereof,

optionally with any two adjacent R^2 groups, or R^6 and the adjacent R^2, forming a buta-1,3-dienyl radical;

y is an integer between 1 and 4, inclusive;

each R^3 is the same or different and is H, halo, hydroxy, lower alkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkyl, or -OQ, where Q is as defined above, optionally with any two adjacent R^3 groups forming a buta-1,3-dienyl radical;

R^5 is as defined for R^3, or, together with R^4, represents a lower alkylene group, a lower alkylenoxy group, a lower alkylenesulphyl group, -S- or -O-;

R^6 is H, or is as defined for R^2, or, together with R^4, forms a trimethylene group or,

together with R^4, forms a buta-1,3-dienyl radical, provided that - - - represents a single bond, R^5 optionally forming a bond to said radical, thereby forming a benzo[a]fluorene nucleus, and wherein any group formed by a combination of R^4 and R^6 is substituted by 0, 1, 2 or 3 R^2 groups;

with the proviso that at least one R^2 or one R^3 is a group -OQ;

R^4 is -CN, $-NO_2$, lower alkyl, lower alkyl substituted by Y, or -Y, in which Y is as defined above;

and pharmaceutically acceptable salts and esters thereof.

2. A compound according to claim 1, wherein - - - represents a double bond.

3. A compound according to claim 2, wherein k = 0.

4. A compound according to claim 1, wherein R^4 and R^5 together form a group as defined, and wherein - - - represents a single bond.

5. A compound according to claim 4, wherein k = 1.

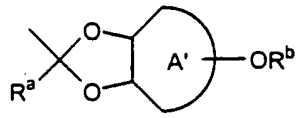
6. A compound according to any preceding claim, wherein R^6 together with R^4 forms a trimethylene group.

7. A compound according to any of claims 1 to 4, wherein R^6 together with R^4 forms a buta-1,3-dienyl radical.

8. A compound according to any of claims 1 to 4, wherein R^6 together with R^4 and R^5 forms a benzo[a]fluorene nucleus.

9. A compound according to any preceding claim, wherein each Q contains from 1 to 20 glycosidic units.

10. A compound according to any preceding claim, wherein at least one Q is an orthoester glycoside having the Formula (II):



(II)

wherein A' represents a glycofuranosyl or glycopyranosyl ring;

R_a is H, C_{1-4} alkyl, C_{7-10} aralkyl, phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, C_{1-4} alkyl or C_{1-4} alkoxy, or is naphthyl; and

R_b is H or a straight or branched chain glycosidic residue containing 1-20 glycosidic units

11. A compound according to any preceding claim, wherein there is only one group OQ.

12. A compound according to any preceding claim, wherein Q is a glycosidic group.

13. A compound according to claim 12, wherein Q is a glycopyranosyl group.

14. A compound according to claim 12, wherein Q is a 1'–β-glucopyranosyl group.

15. A compound according to any preceding claim, wherein there is only one group R^2.

16. A compound according to claim 15, wherein R^2 is a group OQ.

17. A compound according to any preceding claim, wherein there is only one group R^2, and wherein said group is in the 4' position on the ring to which it is attached.

18. A compound according to any preceding claim, wherein R^1 is $-(CH_2)_nCR^5=CR^6CR^7$, n is 1 or 2 and R^5 and R^6 are H.

19. A compound according to claim 18, wherein R^7 is -C(O)OR^{15}.

20. A compound according to claim 18, wherein R^7 is -COOH.

21. A compound according to any preceding claim, wherein R^1 is -X-$(CH_2)_q$- NR^8R^9, X is O.

22. A compound according to claim 19, wherein q = 2.

23.. A compound according to claim 21 or 22, wherein R^8 and R^9 are each methyl or ethyl.

24. A compound according to claim 21 or 22, wherein R^8 and R^9 together with the N to which they are joined, represent a piperidinyl or pyrrolidinyl group.

25. A compound according to any preceding claim, wherein y is 1.

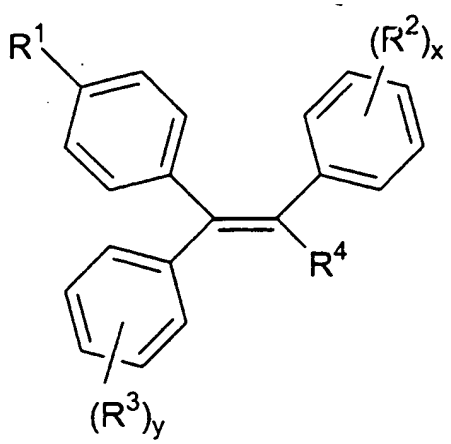
26. A compound according to any preceding claim, wherein R^3 is hydroxy.

27. A compound according to any preceding claim, wherein R^3 is iodo.

28. A compound according to any preceding claim, wherein R^4 is methyl or ethyl.

29. A compound according to any preceding claim, wherein R^4 is a chlorine atom, chloromethyl or chloroethyl group.

30. A compound of Formula (Ia):



(Ia)

wherein

R^1 is: H;

$-(CH_2)_nCR^5=CR^6CR^7$

in which n is a number selected from 0, 1 and 2;

R^5 and R^6 are independently H, $-C_{1-4}$ alkyl, $-C_{2-4}$ alkenyl, $-C_{2-4}$ alkynyl, $-X-C_{1-3}$ alkyl, $-X-C_{2-4}$ alkenyl, $-X-C_{2-4}$ alkynyl or -Y;

X is oxygen or sulphur and Y is halogen, H, alkylcarbonyloxy, formyloxy or formyl;

R^7 is -CN, $-C_{1-4}$alkyl-OH, $-C(O)NR^{10}R^{11}$, $-C(O)NR^{12}R^{13}$, $-C_{1-4}$alkyl-$NR^{10}R^{11}$, $-C(O)R^{12}$, $-C(O)OR^{15}$, $-C(O)NR^{12}OR^{15}$, $-C(O)NHC(O)R^{12}$, $-C(O)NHCH_2R^{12}$, $-C(NH_2)(NOR^{15})$, $-S(O)R^{12}$, $-S(O)(O)(OR^{15})$, $-S(O)(O)N(H)(CO_2R^{15})$, PO_3R^{15}, $-P(O)(NR^{12}R^{13})(NR^{12}R^{13})$, $-P(O)(NR^{12}R^{13})(OR^{14})$, $-CONR^{12}(CH_2)_rOCH_3$, $-CONR^{12}(CH_2)_rNR^8R^9$ or oxadiazole substituted with methyl;

R^8 and R^9 are independently hydrogen, $-C_{1-7}$alkyl, $-C_{3-7}$cycloalkyl, $-O-C_{1-7}$alkyl, $-C_{1-7}$alkyl-Y or phenyl, or, together, form a lower alkylene, a lower heteroalkylene, a lower alkenylene or lower heteroalkenylene group having from 3 to 6 atoms;

R^{10} and R^{11} are independently methyl or ethyl or, taken together, form a morpholino group bonded via its nitrogen atom;

R^{12} and R^{13} are independently H, -C_{1-12}alkyl, -C_{2-12}alkenyl, -C_{2-12}alkynyl, -O-C_{1-12}alkyl, -O-C_{2-12}alkenyl, -O-C_{2-12}alkynyl, -C_{3-7}cycloalkyl, -C_{3-7}cycloalkenyl, linear and cyclic heteroalkyl, aryl, heteroaryl or -Y';

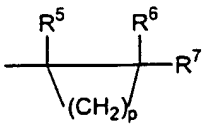
R^{14} and R^{15} are independently hydrogen, -C_{1-12}alkyl, -C_{2-12}alkenyl, -C_{2-12}alkynyl, -C_{3-7} cycloalkyl, -C_{3-7} cycloalkenyl, linear and cyclic heteroalkyl, aryl, or heteroaryl;

r is an integer between 1 and 12, inclusive,

Y' is hydrogen, alkylcarbonyloxy, formyloxy or formyl;

$-(CH_2)_mC(X)NR^8R^9$ or $-Z-(CH_2)_q-NR^8R^9$, in which R^8 and R^9 are as defined above,

Z is oxygen or sulphur, m is the integer 1 or 2 and q is the integer 1 or 2;



in which R^5, R^6 and R^7 are as defined above and p is an integer between 1 and 4, inclusive;

-R-COOH

in which R is $-(CH_2)_tO-$ or $-(CH_2)_u-$ and *t* and *u* each represents an integer between 1 and 4, inclusive; or

$-O-A-S(O)_w-B-R^d$, in which

A is either a direct bond or an amino bridge $-NR^c-$ or $(CH_2)_l-$,

R^c is a hydrogen atom or a straight-chain or branched alkyl group with up to 6 carbon atoms and l is an integer between 1 and 5, inclusive;

w is 0, 1 or 2,

B is either a direct bond or a saturated or unsaturated, aliphatic, linear or branched hydrocarbon chain with up to 6 carbon atoms;

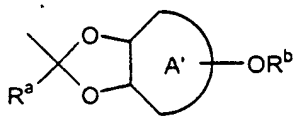
R^d is a hydrogen atom; a partially or completely fluorinated, saturated, aliphatic, linear or branched C_{1-3}-alkyl group; phenyl, or 1- or 2-naphthyl; an amide radical of formula $-C(O)NR^{16}R^{17}$ where R^{16} and R^{17} are identical or different and are a hydrogen atom, a linear or branched C_{1-8}-alkyl radical,

optionally substituted by one or more radicals selected from aryl, alkyl- and dialkylamino, hydroxy, halogen or esterified carboxyl;

x is an integer between 1 and 5, inclusive;

each R^2 is the same or different and represents a halo, hydroxy, lower alkyl or lower alkoxy group, or -OQ,

wherein Q is a straight or branched chain glycosidic residue containing 1-20 glycosidic units, or is an orthoester glycoside moiety of the Formula (II):



(II)

wherein A' represents a glycofuranosyl or glycopyranosyl ring;

R_a is H, C_{1-4} alkyl, C_{7-10} aralkyl, phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, C_{1-4} alkyl or C_{1-4} alkoxy, or is naphthyl; and

R_b is H or a straight or branched chain glycosidic residue containing 1-20 glycosidic units;

or one R^2 is a buta-1,3-dienyl radical which, together with the ring to which it is attached, forms a naphthyl group, with the proviso that at least one of R^2 is a group -OQ;

y is an integer between 1 and 5, inclusive;

each R^3 is the same or different and is H, halo, hydroxy, lower alkyl, or lower alkoxy, or one R^3 is a buta-1,3-dienyl radical which, together with the ring to which it is attached, forms a naphthyl group;

R^4 is -CN, $-NO_2$, lower alkyl, lower alkyl substituted by Y, or -Y, in which Y is as defined above;

and pharmaceutically acceptable salts and esters thereof.

31. A compound according to claim 30, wherein:

R^1 is wherein is -Z-$(CH_2)_q$-NR^8R^9, where q is 2, Z is oxygen, either R^8 is H or a lower alkyl radical and R^9 is a lower alkyl radical, or R^8 and R^9 are joined together with the adjacent nitrogen atom to form a heterocyclic radical;

R^4 is H or lower alkyl;

R^2 is -OQ;

R^3 is H or OH;

or a pharmaceutically acceptable salt hereof.

32. A compound according to claim 31, wherein:

R^8 and R^9 are both the same lower alkyl radical;

R^4 is a lower alkyl radical;

R^2 is -O-glucosyl; and

R^3 is H.

33. A compound according to claim 31 or 32, wherein:

R^8 and R^9 are both methyl; and

R^4 is ethyl.

34. A compound according to claim 1 which is:

1-[4'-(2-dimethylaminoethoxy)phenyl]-1-(4'-0-β-1'-glucopyranosylphenyl)-2-phenylbut-1-ene,

1-[4'-(2-dimethylaminoethoxy)phenyl]-1-(3'-0-β-1'-glucopyranosylphenyl)-2-phenylbut-1-ene,

4-chloro-1-[4'-(dimethylaminoethoxy)phenyl]-1-(4'-0-β-1'-glucopyranosylphenyl)-2-phenylbut-1-ene,

(E)-1-(4-iodophenyl)-2-(4-O-β-1'-glucopyranosylphenyl)-1-[4-(pyrrolidinoethoxy)phenyl]but-1-ene,

1-{4-[2-(diethylamino)ethoxy]phenyl}-2-(4-O-β-1'-glucopyranosylphenyl)-1-phenyl-2-chloroethenylene,

[3,4-dihydro-2-(4-O-β-1'-glucopyranosylphenyl)-1-naphthalenyl]{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}methanone,
11-{4-[2-(1-piperidinyl)ethoxy]phenyl}-11*H*-3-(O-1'-β'-glucopyranosyl)-benzo[a]fluorene-9-ol,
11-{4-[2-(1-piperidinyl)ethoxy]phenyl}-11*H*-benzo-[a]fluorene-3-ol-9-O-β'-glucopyranoside, or
trans-1-{2-[4-(7-O-1'-β-glucopyranosyl-2,2-dimethyl-3-phenyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)phenoxy]ethyl}pyrrolidine.

35. A compound according to any preceding claim, wherein the glycosidic residues are acylated with a group R^{16}–(C=O)-, wherein R^{16} is hydrogen, lower C_{1-6} alkyl, C_{6-10} substituted or unsubstituted aryl or C_{7-16} aralkyl.

36. A pharmaceutical composition comprising a compound according to any preceding claim, together with a pharmaceutically acceptable carrier therefor.

37. A compound according to any of claims 1 to 35, for use in the treatment or prophylaxis of one of the following conditions; cardiovascular disease, osteoporosis, endometriosis, obesity, benign prostatic hypertrophy, prostatic carcinoma, oestrogen-dependent tumours, oestrogen independent tumours, breast cancer, metastatic breast cancer, pre-menstrual syndrome, vasomotor spasms associated with menopause, atrophic vaginitis, Kraurosis vulvae, female hypogonadism, primary ovarian failure, excessive hair growth, and psoriasis.

38. A compound according any of claims 1 to 35, for use in the treatment or prophylaxis of an oestrogen-dependent tumour.

39. A compound according any of claims 1 to 35, for use in the treatment or prophylaxis of a breast tumour.

40. Use of a compound according to any of claims 1 to 35 in the manufacture of a medicament for use as defined in any of claims 34 to 37.

41. Use according to claim 40, wherein the medicament is adapted for oral administration.

Serum 4-OH-Tamoxifen in Rats after receiving last dose of:
Tamoxifen, 4-OH-Tamoxifen or 4-OH-Tamoxifen-G

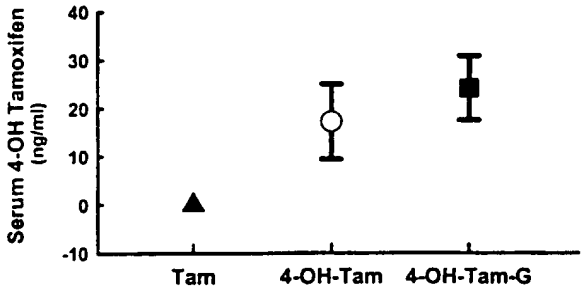


Figure 1

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/GB 00/03865

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H15/203 C07H15/26 A61K31/70 A61P35/00 A61P19/10
A61P25/00 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2001	19/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scott, J

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Inten nal Application No
PCT/GB 00/03865

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